Neurophysiological follow-up of two siblings with Crigler-Najjar syndrome type I and review of literature

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Crigler-Najjar syndrome type I is an autosomal recessive inherited disease and rarely seen in childhood. Bilirubin neurotoxicity is the morbidity of the disease due to the elevated unconjugated bilirubin levels. Mental retardation, seizures, cognitive dysfunction, oculomotor nerve palsy, ataxia, choreoathetosis, and spasticity may be seen. Due to the high bilirubin levels, alterations in the neurophysiological studies may be detected. In this study, we describe two siblings who were diagnosed with Crigler-Najjar syndrome type I who underwent a successful liver transplantation using a single cadaveric organ, together with their neurophysiological follow-up and review of the literature.

Key words: Crigler-Najjar syndrome, bilirubin neurotoxicity, neurophysiological studies, children.

Crigler-Najjar (CN) syndrome type I is a rare, autosomal recessively inherited disorder that is characterized by unconjugated hyperbilirubinemia from birth[1,2]. As a result of the complete absence of the hepatic UDP-glucuronosyltransferase enzyme, unconjugated bilirubin levels elevate in the blood and pose a risk of neurotoxicity[3].

Crigler-Najjar (CN) syndrome is usually diagnosed in the neonatal period and requires liver transplantation[4]. The syndrome is clinically classified as type I and type II, based on the bilirubin levels, presence of kernicterus and response to phenobarbital and other UDP-glucuronosyltransferase enzyme-inducing agents[5]. In CN type II patients, phenobarbital treatment reduces serum bilirubin levels by 30% due to the induction of the residual UDP-glucuronosyltransferase enzyme, whereas only a minor effect is observed in CN type I patients[6].

Unconjugated bilirubin is the breakdown product of heme and is neurotoxic. Severe neonatal hyperbilirubinemia is associated with kernicterus[7]. Mental retardation, oculomotor nerve palsy, ataxia, choreoathetosis, spasticity, and sensorineural hearing loss can develop due to the elevated serum bilirubin levels[2].

Here, we present a boy and his sister diagnosed with CN syndrome type I along with their neurophysiologic follow-up and review of the literature regarding the neurophysiological findings of this rare disease.

Case Reports

Case 1

A 14-year-old boy admitted to our hospital with complaints of jaundice, weakness, speech difficulty, movement disorders, fecal incontinence, and mental deterioration. He was born to third-degree consanguineous parents after a full-term pregnancy, and his birth weight was 3700 g. The patient had developed jaundice soon after birth, requiring phototherapy and exchange transfusion. During childhood, he had been treated irregularly with phototherapy and long-term oral phenobarbital. According to his parents, his development was normal until the age of 12 years. He had received no treatment for the last two years because of compliance issues. His complaints started following a febrile upper respiratory tract infection. His neurologic examination revealed dysmetric movements of upper

limbs, gait disturbances, ataxic movements of both legs, dysdiadochokinesia, and slow and dysarthric speech. Babinski reflexes were plantar flexion, and deep tendon reflexes were normal. Laboratory analyses revealed total serum bilirubin as 47.5 mg/dl and direct bilirubin as 0.8 mg/dl. Serum transaminases were normal. The patient was treated with combined phototherapy (12 hours per day) and cholestyramine. During the phototherapy, his serum bilirubin levels decreased from 47.5 to 29.1 mg/dl. While a therapeutic trial with oral administration of phenobarbital at a dosage of 5 mg/kg/day was not efficient, total serum bilirubin concentrations ranged from 32.5 to 31.8 mg/dl. The blood bilirubin to albumin concentration ratio was >0.7. The diagnosis of the CN syndrome type I was made based on the medical history, biochemical results and lack of response to the phenobarbital treatment. Brain magnetic resonance imaging (MRI) and abdominal ultrasonography (USG) findings of the patient were normal. An electroencephalography (EEG) showed 10-12 alpha background activity associated with generalized high amplitude slow waves, right hemisphere predominant. In the initial evaluation, visual evoked potential (VEP) and brain auditory evoked potential (BAEP) tests could not be performed due to patient non-compliance. Two months later, the patient underwent a successful liver transplantation using a single cadaveric organ with a significant reduction in bilirubin levels. Following the transplantation, he was chronically treated with tacrolimus. Detailed neurologic examination, EEG, VEP, and BAEP were performed every six months during the two-year follow-up period. The EEG improved four months after the liver transplantation and was found to be completely normal. VEPs revealed elevated P100 latencies four months after the liver transplantation. During the neurophysiologic follow-up, BAEPs did not show any abnormalities. The bilirubin level decreased to normal values; however, neurobehavioral dysfunction and VEPs of the patient did not improve.

Case 2

A seven-year-old girl presented with the complaint of jaundice from birth. She was born after a full-term normal pregnancy with a birth weight of 3500 g. She became jaundiced on the first day of life. She was treated with phototherapy and long-term oral phenobarbital treatment at various hospitals. There was no history of exchange transfusion. According to her parents, she had received no treatment for the last two years. Neurologic examination results were normal. Brain MRI and abdominal USG findings were normal. Laboratory analyses revealed total serum bilirubin as 39.7 mg/dl and direct bilirubin as 0.7 mg/dl. Serum transaminases were normal. She was treated with phototherapy (12 hours per day) and cholestyramine. During the phototherapy, her serum bilirubin levels decreased from 39.7 to 22.9 mg/dl. Oral administration of phenobarbital at a dosage of 5 mg/kg/day was not efficient, and total serum bilirubin concentrations ranged from 26.9 to 26.4 mg/dl. The diagnosis of the CN syndrome type I was made based on her medical history, biochemical results and the lack of response to phenobarbital treatment. Two months later, the patient underwent a liver transplantation at the same time as her brother using single cadaveric organ with a significant reduction in bilirubin levels. She was chronically treated with tacrolimus after the transplantation. EEG, VEP and BAEP were performed every six months during the two-year follow-up period. Before and after the liver transplantation, EEG, VEPs and BAEPs of the patient were normal. The patient developed post-transplant lymphoproliferative disease eight months after surgery, and achieved remission after chemotherapy.

Discussion

Without treatment, CN syndrome type I is a lethal metabolic disorder from which patients die at an early age. The most important cause of morbidity in CN syndrome is the bilirubin neurotoxicity, and the patients are at increased risk for neurologic deficits[8]. Kernicterus or bilirubin encephalopathy generally develops in infants and children due to the accumulation of unconjugated bilirubin in the brain. However, patients with CN syndrome may also experience bilirubin encephalopathy in adulthood[9].

Before the introduction of phototherapy in 1958, the majority of patients died with kernicterus during the neonatal period[10]. Phototherapy transforms unconjugated bilirubin into several

photo isomers that can be excreted rapidly. The potency of phototherapy depends on the intensity and wavelengths of the phototherapy lights[11]. Since 1958, phototherapy, heme oxygenase inhibitors, exchange transfusion, liver transplantation techniques and hepatocyte transplantation have been used to treat CN type I, and the life expectancy of the patients has increased[6,12]. Liver transplantation was first conducted in 1986 by Kaufman et al.[13] Gene therapy for CN syndrome type I has been discussed in recent decades. Viral and non-viral vectors have been used to prevent hyperbilirubinemia in animal models, and it has been demonstrated that long-term normalization of serum bilirubin levels can be achieved by gene therapy; however there has been no clinical trial in CN patients[14,15].

Bilirubin is a product of heme catabolism and requires glucuronidation for excretion from blood. If there is a complete deficiency in bilirubin glucuronidation, CN syndrome type I occurs, and unconjugated bilirubin accumulates in the blood[11]. Brain damage due to the bilirubin toxicity has a typical distribution involving the hippocampus, corpus striatum, globus pallidus, and putamen[16]. The mechanism of the bilirubin neurotoxicity and why bilirubin accumulates in specific areas of the brain are still not fully understood[11,17]. The possible mechanisms of the neurotoxicity are inhibition of the phosphorylation and dysfunction of the respiratory chain in the mitochondria[18]. High levels of bilirubin produce apoptosis and necrosis of the neurons due to the mitochondria dysfunction[19].

The first signs of acute bilirubin encephalopathy in the neonatal period are hypotonia and poor sucking reflex. Subsequently, opisthotonos and hypertonia develop[20]. In a prospective study, the incidence of kernicterus was 0.9/100000 live births in the United Kingdom and Ireland[21]. With aging, the risk of neurodevelopmental abnormalities increases[22]. Unfortunately, no such statistical data are yet available for our country. Chronic bilirubin encephalopathy has a mortality rate of 10% and a morbidity rate of 70%[23]. Wennberg et al.[24] concluded that increased total serum bilirubin levels (≥25 mg/dl) had very low specificity for predicting kernicterus, with a sensitivity of 92%.

As a result of bilirubin toxicity in the central nervous system, kernicterus, cognitive dysfunction, extrapyramidal dysfunction, choreoathetosis, ataxia, tremor, and behavioral modifications may be seen[25]. Basal ganglia and cerebellar and hippocampal structures are usually affected by elevated bilirubin levels in the brain[25]. Shevell et al.[25] concluded that the cerebellar and hippocampal regions of the brain are vulnerable in adolescence, while the basal ganglia are vulnerable in infancy. Kernicterus is usually symptomatic in the neonatal period; cognitive and extrapyramidal dysfunction usually occurs early in the second decade, and cerebellar dysfunction signs become symptomatic especially in adolescence[25,26]. Cerebellar symptoms rarely appear as the presenting manifestations of CN syndrome type[18,26]. In our study, the cranial MRI scans of both patients were normal.

Normal neurodevelopment prior to liver transplantation has been reported in CN syndrome type I patients in numerous case reports[3,25]. Strauss et al.[3] reported 20 patients with CN syndrome type I. They concluded that early recognition of hyperbilirubinemia and effective phototherapy make exchange transfusions unnecessary, and phototherapy can prevent the development of brain injury until liver transplantation becomes possible[3].

Due to the high bilirubin levels, alterations in BAEPs may be seen[27]. BAEPs can detect previous brain injuries as a result of the hyperbilirubinemia. Decreased amplitudes and loss of waves III and V can be seen as a result of elevated bilirubin levels. Wave I abnormalities are also seen with very high bilirubin levels and kernicterus. After the phototherapy and/or exchange transfusion treatments, BAEP abnormalities usually reverse to normal values in several months[28,29]. A retrospective study with 12 infants who suffered severe neonatal jaundice and bilirubin toxicity showed that 3/9 (33.3%) of the patients had abnormal VEPs and 7/10 (70%) had BAEP abnormalities. In the five patients studied, all had EEG abnormalities including multifocal and generalized spikes and polyspikes. Two of four (50%) patients had abnormal MRI findings consistent with kernicterus. On the neurologic follow-up, four of 12 patients had hypertonia, five had hypotonia, and three had athetosis. Gaze palsy was seen in a minority of the patients[30]. Maisels

et al.[31] reported the presence of vertical gaze palsy in 90% of the 22 cases who had posticteric encephalopathy. Electroencephalographic and VEP abnormalities can also be seen in increased bilirubin levels. Gurses et al.[32] concluded that hyperbilirubinemia affects the electrical activity of the brain, and they found significantly higher delta frequency and lower theta, beta and alpha frequencies compared to the control group in patients with unconjugated hyperbilirubinemia. Perretti et al.[33] reported the electrophysiological evaluation of 10 CN syndrome patients (4/10 CN type I) (mean age: 18±4 years). In that study, the EEG of a patient normalized one year after liver transplantation, and VEPs showed increased P100 latencies in 3/4 of the CN syndrome type I patients. They did not detect any BAEP abnormalities in the follow-up evaluations. In light of these results, they concluded that EEG and VEPs may help in the decisional process for liver transplantation before the brain damage occurs[33]. Even though there was a strong relationship between EEG abnormalities and bilirubin levels, our second patient's EEG was normal before the liver transplantation[22]. Both of our patients' BAEPs were normal during the follow-ups[22,33]. According to the literature, in CN syndrome type I patients, VEP abnormalities are seen several years after liver transplantation, and in our first case, we detected abnormal VEP results 18 months after the liver transplantation[22,34].

In conclusion, neurologic abnormalities are usually irreversible despite the decreased levels of unconjugated hyperbilirubin following liver transplantation. Liver transplantation should be performed before neurobehavioral abnormalities occur. EEG and VEPs are important tests in terms of identifying and managing the neurotoxic effects of severe hyperbilirubinemia in CN syndrome type I patients and also for decision-making regarding liver transplantation.

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